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The hepatectomy efficacy of huge hepatocellular carcinoma and its risk factors

A meta analysis

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Abstract

Background: There has always been a controversy on the hepatectomy for huge hepatocellular carcinoma (HCC). Therefore, we aim to explore the hepatectomy efficacy of huge HCC and its risk factors.

Methods: A systematic research was performed using PubMed, MedLine, Web of Knowledge, and Cochrane Library from their establishment to August 2017. The major endpoints were overall survival (OS) rate and recurrence-free survival (RFS) rate, and the secondary ones were the morbidity of complications and mortality of hepatectomy.

Results: About 13 studies with a total of 7609 patients were included in this meta-analysis. The hepatectomy efficacy of huge HCC was inferior to non-huge HCC both in OS (hazard ratio [HR] = 2.18, 95% confidence interval [*CI*] = 1.90–2.50, $P < .00001$; $I^2 = 66\%$, $P = .003$) and RFS (HR = 1.97, 95% *CI* = 1.76–2.19, $P < .00001$; $I^2 = 74\%$, $P = .0001$). However, the risk difference[RD] of the 1-year, 3-year and 5-year OS tended to be acceptable (RD = −0.05, 95% *CI* = −0.11–0.00, $P = .05$; RD = −0.13, 95% *CI* = −0.21–−0.05, $P = .002$; RD = −0.10, 95% *CI* = −0.19–−0.01, $P = .03$; respectively). Moreover, there were also no significant differences between huge HCC and non-huge HCC in the morbidity of complication and mortality of hepatectomy (RD = 0.07, 95% *CI* = −0.09–0.23, $P = .38$; RD = −0.01, 95% *CI* = −0.00–−0.03, $P = .06$; respectively). Related risk factors were measured to explore the differences, and the results showed that the level of alpha fetal protein (AFP) and the margin-positive rate were higher (standard mean difference [SMD] = 0.57, 95% *CI* = 0.26–0.88, $P = .0003$; odd radio[OR] = 32.52, 95% *CI* = 1.02–6.22, $P = .04$; respectively), the characteristic of huge HCC tended to be worse such as lower clinical or pathological stage, incomplete capsule and incorporate satellite metastases (OR = 2.91, 95% *CI* = 1.68–5.04, $P = .001$; OR = 3.99, 95% *CI* = 3.40–4.67, $P < .00001$; OR = 2.52, 95% *CI* = 1.66–3.83, $P < .0001$; respectively), and the rate of micorvascular invasion (MVI) including portal vein tumor thrombus (PVTT) were higher (OR = 3.36, 95% *CI* = 1.61–7.02, $P = .001$; OR = 2.75, 95% *CI* = 2.29–3.31, $P < .00001$; respectively) in the huge HCC.

Conclusion: The hepatectomy efficacy of huge HCC was inferior to non-huge HCC, but its survival benefits and feasibility were confirmed in this meta-analysis. In addition, higher level of AFP, positive margin, lower clinical or pathological stage, incomplete capsule, incorporate satellite metastasis and MVI were significantly correlated with poor OS.

Abbreviations: DFS = disease-free survival, HCC = huge hepatocellular carcinoma, MVI = micorvascular invasion, OS = overall survival, RFS = recurrence-free survival.

Keywords: hepatectomy, huge hepatocellular carcinoma, meta-analysis

1. Introduction

Hepatocellular carcinoma (HCC) is one of the most common cancer in the world.[1] With the development of comprehensive therapy including locoregional and systemic treatment, HCC has not more than a lethal cancer, especially in eastern Asia.[2] Up to now, surgical resection has been considered as the most efficient therapy.[3] While, as for huge HCC (i.e., >10 cm in diameter), it is hard to say.

Firstly, huge HCC is the absolute contraindication of the liver transplantation.[4] Secondly, radiofrequency ablation (RFA)[5] and trans-arterial chemoembolization (TACE)[6] has been proved to be of little efficacy. Moreover, Sorafenib, as the only therapeutic targeted drug approved by the FDA, could not achieve tumor regression.[7] Hence, surgical resection is the only option for huge HCC.

In this meta-analysis, not only the efficacy of hepatectomy of huge HCC was evaluated, but also the safety and feasibility were assessed. And in addition, the risk factors associated with the results were also analyzed.

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2. Material and methods

2.1. Literature search

A comprehensive search was conducted to clarify all the published researches of hepatectomy on huge HCC versus non-huge HCC. Both English electronic databases such as PubMed, MedLine, the Cochrane Library, Web of Knowledge, and Chinese databases including Wan Fang, CNKI, and SinoMed were used to seek the literature, from September 1990 to September 2017. Keywords including "hepatocellular carcinoma " and "hepatectomy" combined with free text words such as "huge" or "giant" or "larger more than 10 cm" or "≥10 cm in diameter" appeared in the electronic search.

2.2. Selection criteria

Huge HCC was defined as the diameter of the HCC tumor exceeding 10 cm.

Inclusion criteria: ① cohort studies and randomized controlled trials were both considered; ② hepatectomy for huge HCC and non-huge HCC; ③ survival was analyzed in the study; ④ sufficient data such as the baseline of characteristic were depicted.

Exclusion criteria: ① in vitro or animal studies; ② case reports, letters, reviews and conference reports; ③ studies based on overlapping cohorts derived from the same center; ④ sample size was not more than 10.

In case of results reported from the same center more than once, the latest was extracted.

2.3. Data extraction

All data were extracted and assessed by 2 independent investigators with predefined forms such as baseline characteristics and outcomes from each study. In the case of disagreement, a third investigator intervened for a conclusion. Hazard ratios (HRs) of overall survival (OS) and recurrence-free survival (RFS) were calculated according to Tierney' algorithm.[8]

2.4. Intervention definition

Partial resection was divided into anatomical and nonanatomical resection according to whether compliance with anatomical structure, minor and major hepatectomy according to the size of the liver resection, and open and laparoscopic hepatectomy according to whether performed by laparoscope.

Minor hepatectomy was defined as the liver resections <3.

Major hepatectomy was defined as the liver resections no fewer than 3.

2.5. Quality assessment

Cohort studies were assessed by Newcastle–Ottawa scale (NOS),[9] and studies scored as ≥ 6 were considered high quality.[10]

2.6. Statistical analysis

The systematic review and meta-analysis were registered at http://www.researchregistry.com and performed using RevMan Version 5.3. HR was applied as a summary statistic for time-to-event outcomes like OS and RFS, odd ratio (OR) was for the dichotomous outcomes and standard mean difference (SMD) was for the continuous outcomes, and all the results followed with 95% confidence intervals (CI). The χ^2 test and I^2 statistics were used to assess the heterogeneity; $P<.05$ or $I^2>50\%$ were considered as significant heterogeneity. When the hypothesis of homogeneity was not rejected, the fixed-effects model was used to estimate the case with homogeneity, and the random-effects model was used for the cases with significant heterogeneity.[10]

3. Results

3.1. Search

Initially, 324 reports were identified initially by 2 independent reviewers including both English and Chinese. A total of 18 articles were excluded after duplicate removal by NoteExpress 3.1. After browsing the titles and abstracts, 283 records were excluded. Among the remaining 13 articles,[11–23] one record was excluded for lack of enough cases.[13] So, there were 12 reports included in this meta-analysis.[11,12,14–23] In total, 7049 patients were enrolled in this meta-analysis, with 1770 cases in the huge HCC group and 5279 cases in the with non-huge HCC group (Fig. 1)

3.2. Trial characteristics

The characteristics and quality of the included trials are shown in Table 1. All the 12 studies included huge HCC group and non-huge HCC group. Follow-up was not mentioned in 1 study, and the remaining had complete follow-up (Table 1). Except for one study, risk factors such as gender, age, preoperative AFP level, tumor characteristic and vascular invasion and so on were involved in all the 12 studies. All the studies included in this meta-analysis were nonrandomized studies and were assessed by NOS. The scores ranged from 7 to 8, indicating that all the studies were high quality (Table 1).

3.3. Long-term outcome of hepatectomy for huge HCC and non-huge HCC

Long-term outcome of hepatectomy including OS and RFS rates were reported in the nine studies, and there were significantly differences in the rate of OS (HR = 2.18, 95% CI = 1.90–2.50, $P<.00001$; $I^2=66\%$, $P=.003$. Fig. 2A) and RFS (HR = 1.97, 95% CI = 1.76–2.19, $P<.00001$; $I^2=74\%$, $P=.0001$. Fig. 2B) between huge HCC group and non-huge HCC group. And, there were also significantly decreases in the 1-year, 3-year, and 5-year OS (75% vs 90%, $P=.002$; 52% vs 74%, $P=.002$; 40% vs 60%, $P=.03$; respectively) and RFS (46% vs 73%, $P<.0001$; 30% vs 47%, $P<.00001$; 20% vs 35%, P = .0002; respectively. Tables 2 and 3). However, the RDs were considerably small (ranged from −0.20 to −0.05, Table 3), which meant that the long-term outcome of hepatectomy for huge HCC was acceptable.

3.4. Short-term outcome of hepatectomy for huge HCC and non-huge HCC

Short-term outcome of hepatectomy was assessed by treatment-related complications and hepatectmoy mortality. And, there were no significant differences in the rates of treatment-related complications (RD = 0.07, 95% CI = −0.09–0.23, $P=.38$; $I^2=66\%$, $P=.05$, Fig. 3A) and hepatectmoy mortality (RD = 0.01, 95% CI = −0.00–0.03, $P=.06$; $I^2=30\%$, $P=.22$, Fig. 3B) between huge HCC group and non-huge HCC group.

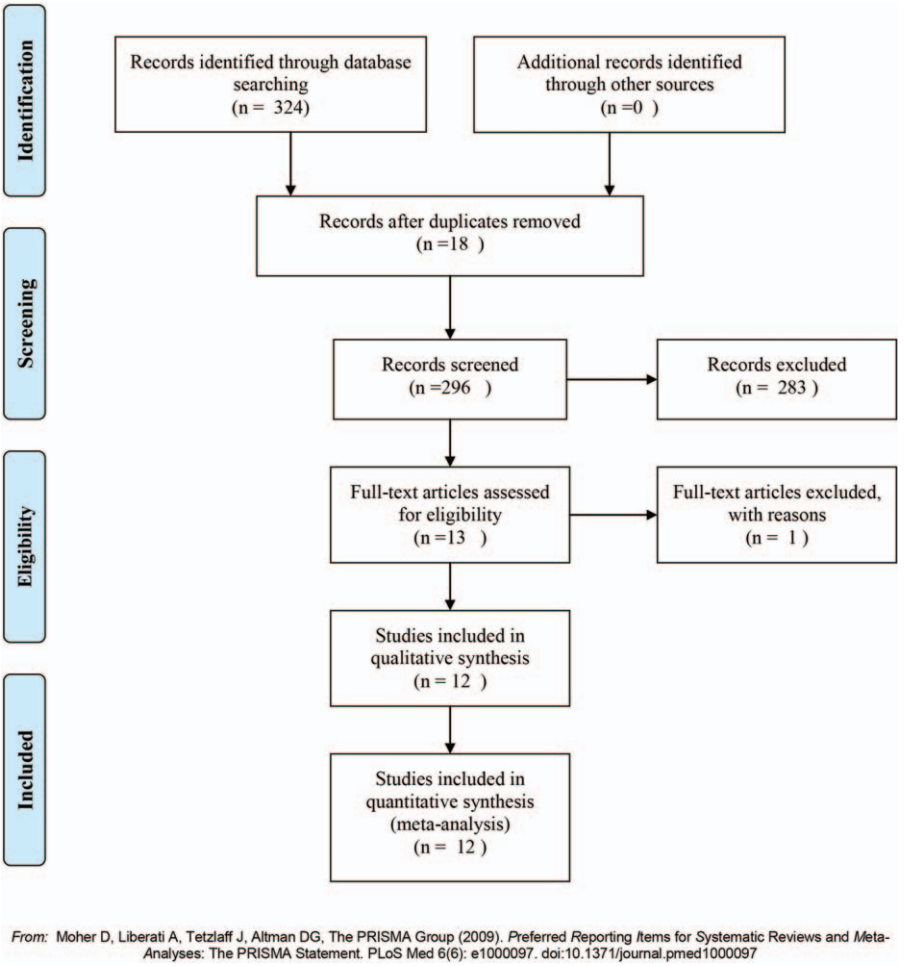

Figure 1. Flowchart of study selection process for meta-analysis.

Table 1

Characteristics of trials included.

				Huge HCC						Non-huge HCC							
Study	Location	Study years	Follow-up, months	Tumor size, cm	HBV, %	Cirrohosis, %	CP (A:B\C)	Solitar: Mulitary	Resection (Major:Minor)	Tumor size, cm	HBV, %	Cirrohosis, %	CP (A:B\C)	Solitary: Mulitary	Resection (Major:Minor)	Outcome indicators	NOS
Waka, 2016	Japan	1990–2013	57	12.4±3.7	39.6	–	53 49:4	36:17	41:12	4.0+2.1	38.4	–	521 511:18	371:150	100:421	OS/RFS	8
Lim, 2014	Japan	1994–2010	53.4	13 (10.5–23)	–	17.1	41 31:10	–	26:15	3.9 (0.8–10)		49.6	560 499:76	–	60:515	OS/RFS	8
Allemann et al, 2013	Switzerland	1997–2009	24/25	13.5 (10–21)	29.3	40.9	22 22:0	–	17:5	4.9 (1–9)	21.9	77.2	79 75:4	–	40:39	OS/DFS	7
Zhang, 2013	China	2002–2010	61.7	>10			81			≤10			528			OS/RFS	8
Jo, 2011	Korea	1994–2009	30	14.5±4.1	72.7	36.4	11 11:0	–	11:0	3.8±2.1	57.5	40 92.5	35:7	–	10:30	OS/DFS	8
Miyoshi et al, 2009	Japan	1987–2004	48.2	10-20		22.7	22 19:3	–	16:6	1.0–9.5		230 49.6	140:90	–	52:178	OS/DFS	7
Taniai et al, 2008	Japan	1987–2006	33.6	13.5±2.8	20.7	41.4	29 23:6	–	15:14	3.7±1.9	14.8	291 53.6	209:82	–	56:235	OS/DFS	8
Liau et al, 2005	USA	1985–2002	27	14.7±4.1		10	82 73:9	71:11	–	6.1±2.5		111 37.0	104:7	101:10		OS/DFS	8
Zhou et al, 2003	China	1964–1999	–	1217						2337						OS	7
Wu et al, 2003	China	1990–1999	12–120	>10	75.5	81.6	– 68	735:492	–	≤10	77.0	87.3 34	–	1772:577		OS	7
Poon et al, 2002	China	1991–2000	56/52	10-32	75.0	79.4	120 51:17	45:23	–	≤10	79.4	368 70.6	28:6	25:9		OS/DFS	8
Shim 2007	Canada	1993–2004	34	13.8±3.0	85.8	26.7	– 24	79:41	108:12	5.4±2.6	84.5	55.2 165	–	287:81	212:156	OS/DFS	8
				13.1±2.9	37.5	–	24:0	–	–	4.7±2.2	44.2	–	145:14	–			

"–" = not mentioned, CP = Child–Pugh score, DFS = disease-free survival, HBV = hepatitis B virus, HCC = huge hepatocellular carcinoma, NOS = Newcastle–Ottawa scale, OS = overall survival, RFS = recurrence-free survival or relapse-free survival.

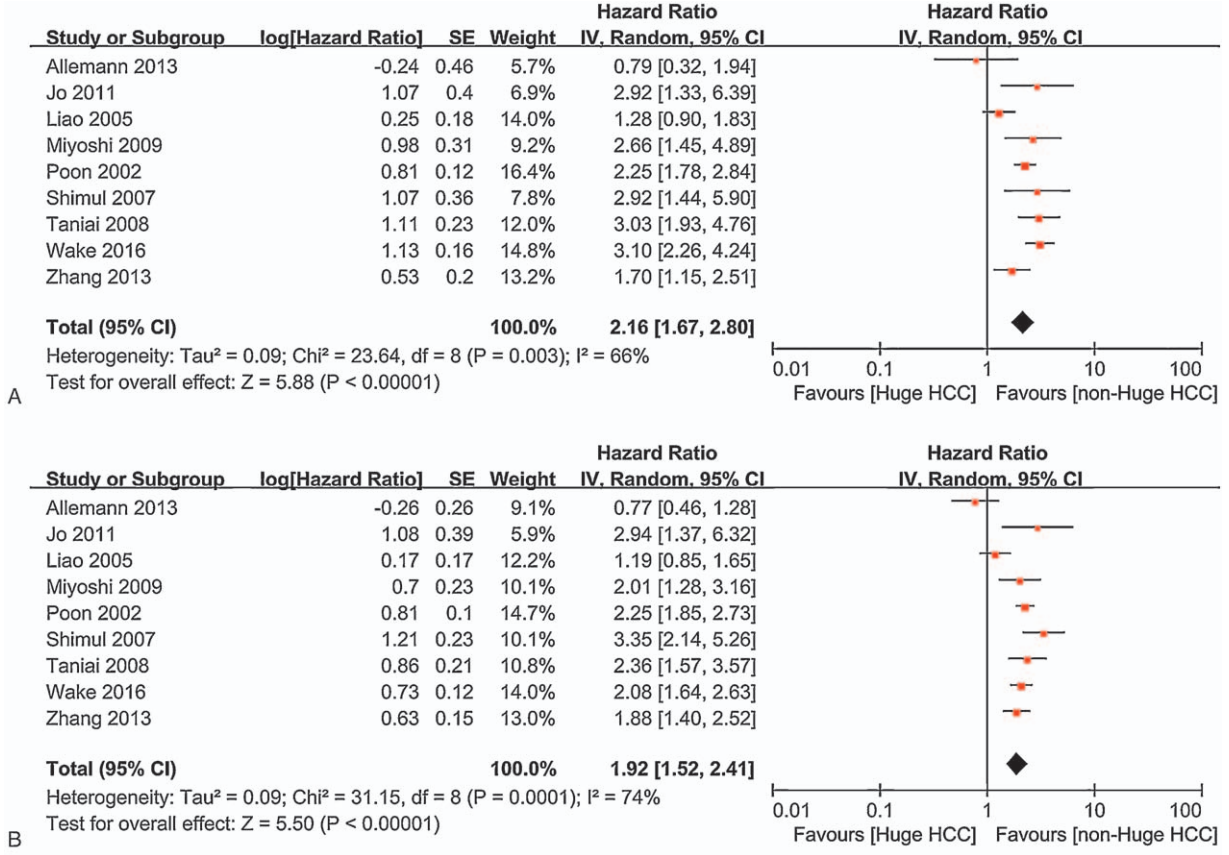

Figure 2. Long-term outcome of hepatectomy for huge HCC and non-huge HCC. HCC = huge hepatocellular carcinoma.

Table 2

The comparison of 1-year, 3-year, 5-year OS or RFS between huge HCC and non-huge HCC.

		Studies included	Participants	Rate (huge vs non-huge)	EM	RD	95%CI	*P*
OS	1-year	11	3495	75% vs 90%	Random	−0.11	−0.18–0.04	.002
	3-year	11	3495	52% vs 74%	Random	−0.13	−0.21–0.05	.002
	5-year	11	3495	40% vs 60%	Random	−0.10	−0.19–0.01	.03
RFS	1-year	10	3393	46% vs 73%	Random	−0.20	−0.29–0.11	<.001
	3-year	10	3393	30% vs 47%	Random	−0.17	−0.24–0.09	<.001
	5-year	10	3393	20% vs 35%	Random	−0.11	−0.17–0.04	.002

CI = confidence interval, EM = effect model, OS = overall survival, RD = risk difference, RFS = recurrence-free survival or relapse-free survival.

Table 3

Risk factors of the hepatectomy efficacy of huge hepatocellular carcinoma.

	Studies included	Participants	EM	OR/SMD	95%CI	*P*
Preoperative AFP	4	1111	Random	0.57	0.26–0.88	<.001
Positive margin	6	2311	Random	2.52	1.02–6.22	.04
Tumor characteristic						
Worse classification	6	1851	Fixed	2.91	1.68–5.04	.001
Incomplete capsule	4	3913	Random	3.99	3.40–4.67	<.001
Combined satellite nodules	4	1112	Random	2.52	1.66–3.83	<.001
Vascular invasion						
MVI	9	2762	Random	2.52	1.02–6.22	.001
PVTT	4	4482	Fixed	2.75	2.29–3.31	<.001

AFP = alpha fetal protein, CI = confidence interval, EM = effect model, MVI = micorvascular invasion, OR = odds ratio, OS = overall survival, PVTT = portal vein tumor thrombus, RFS = recurrence-free survival or relapse-free survival, SMD = std, mean difference.

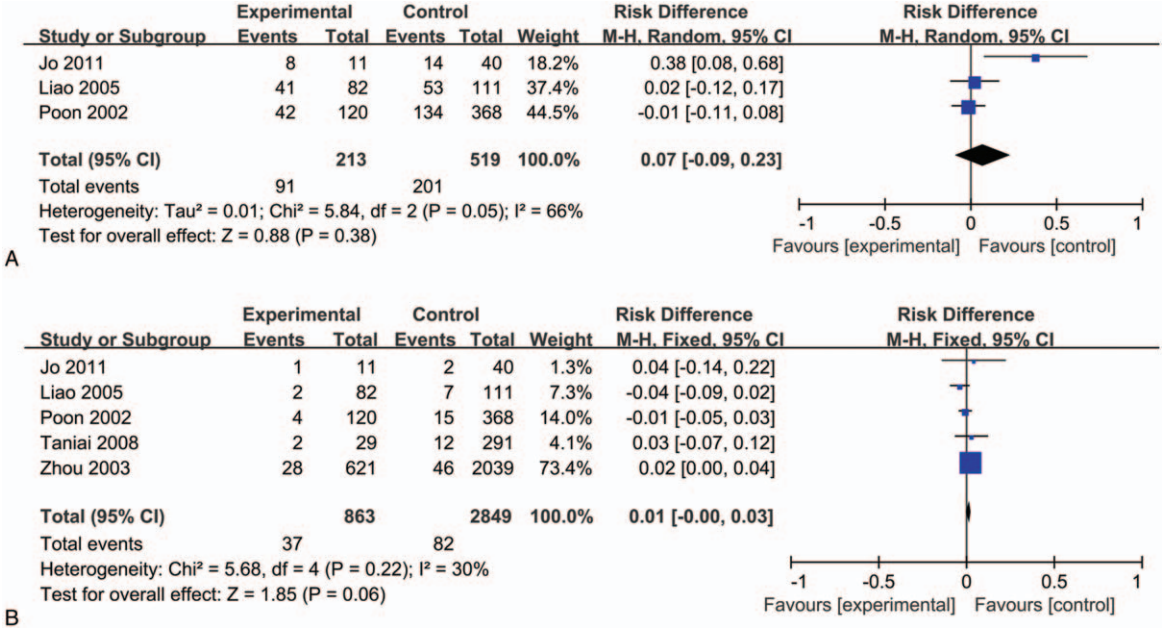

Figure 3. Short-term outcome of hepatectomy for huge HCC and non-huge HCC. HCC = huge hepatocellular carcinoma.

3.5. Risk factors of hepatectomy for huge HCC and non-huge HCC

Risk factors such as gender, age, tumor characteristic and so on were analyzed. Results showed that as for the hepatectomy, there were significant differences in the preoperative AFP levels (SMD = 0.57, 95% *CI* = 0.26–0.88, *P* = .0003), the rate of positive margin (OR = 32.52, 95% *CI* = 1.02–6.22, *P* = .04), the rate of worse classification (OR = 2.91, 95% *CI* = 1.68–5.04, *P* = .0001), the rate of incomplete capsule (OR = 3.99, 95% *CI* = 3.40–4.67, *P* < .00001), the rate of combined satellite nodules (OR = 2.52, 95% *CI* = 1.66–3.83, *P* < .0001), the rate of MVI (OR = 2.52, 95% *CI* = 1.66–3.83, *P* = .001), and the rate of PVTT (OR = 2.75, 95% *CI* = 2.29–3.31, *P* < .00001) between huge HCC group and non-huge HCC group (Table 3).

3.6. Sensitivity analysis

Significant heterogeneities were observed among the included studies for OS and RFS rate. The studies conducted by Liau et al[19] and Allemann et al[14] showed results were significantly different from others, which likely contributed to the heterogeneities. After excluding these two studies, the pooled HRs for OS rate and RFS rate using the fixed-effect model were 2.47 (95% *CI* 2.13–2.86, *P* < .00001; I^2 = 18%, *P* = .29) and 2.21 (95% *CI* 1.96–2.48, *P* < .00001; I^2 = 0%, *P* = .47), respectively.

4. Discussion

Hepatectomy is still the most effective therapy for the huge HCC,[12] although the clinical value has always been questioned. In this meta-analysis, the feasibility and efficacy of hepatectomy for huge HCC has been demonstrated by evidence-based medicine.

It is prerequisite for the feasibility of hepatectomy. Tumor size was used to be the restriction of hepatectomy for HCC.[24–26] Hwang et al[27] found that it was resectable for huge HCC, and the rate of anatomical hepatectomy and R0 resection were 91.9% and 89.4%, respectively. Compared with the non-huge HCC, the patients of huge HCC tended to be younger epidemiologically and rarely combined with serious cirrhosis. Hence, it is absolutely feasible of hepatectmoy for huge HCC, especially for those young patients with favorable liver function.

It is essential to evaluate the efficacy of hepatectomy for huge HCC. A propensity score analysis showed that hepatectomy for large HCC (>5 cm in diameter) including huge HCC was superior to local-regional therapy. Similarly, the efficacy of hepatectomy for large HCC including huge HCC was reported to superior to TACE in the latest meta-analysis. And, exceeding two liver sections was considered to be independent prognostic factor for huge HCC. In this meta-analysis, we found that the rates of 1-year, 3-year, and 5-year OS were 75%, 52%, and 40%, which were acceptable, although they were significantly lower than those of non-huge HCC.

Safety is the key of hepatectomy for huge HCC. Severe complications did not increase after hepatectomy, compared with local-regional therapy such as TACE.[28,29] On the other hand, the median mortality was reported to be 3.5% in a systematic review,[30] which was much lower in the latest report.[31] In this meta-analysis, there were no significant differences on the postoperative complications and mortality between huge HCC group and non-huge HCC group, which indicated that it was safe to perform hepatectomy for huge HCC.

Based on these above, huge HCC was not considered to be a contraindication for hepatectomy. However, the criteria should not be expanded unlimitedly. Both tumor characteristic such as classification, capsule, and operative variables including intraoperative estimated blood loss,[32] anatomical or non-anatomical hepatectomy[33–35] were reported to be risk factors of hepatectomy for huge HCC. Other factors including AFP dynamic changes,[36] MVI,[37] and cirrhosis[38] were also considered to affect the efficacy of hepatectomy seriously. All of the risk factors were enrolled in this meta-analysis, and results showed that in the huge HCC group, the level of preoperative AFP was higher, the rate of positive margin increased, the tumor characteristic tended to be worse including lower classification, incomplete capsule and combined satellite nodules, and the incidence of MVI and

PVTT increased, too, compared with non-huge HCC. And therefore, it should be prudent for us to conduct hepatectomy for huge HCC patients accompanied with such factors.

There were several limitations in this study. First, there were no RCTs included in this meta-analysis, which made the conclusion sound weaken because cohort data had selection bias. Second, survival data such as OS and DFS/RFS were extracted from survival curves, which might be brought with several tiny errors. Third, the definition of MVI varied due to the lack of a golden standard.[39–41] Fourth, measurement data and enumeration data were mixed up to record the same variable such AFP level.[11,12,15,16] Fifth, the baseline characteristics varied from each other, caution should be taken when interpreting these results. Finally, it was hard to avoid publication bias, because the journals tend to publish positive results.

5. Conclusion

In summary, we concluded that hepatectomy for huge HCC was feasible and effective in this meta-analysis. And, the survival will be improved in the future with the advent of precision hepatectomy, administration of newly targeted drugs and combination with systematic therapy. However, hepatectomy is not suitable for all the huge HCC patients, criteria should be worked out in future, and related risk factors should be taken into consideration.

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